REMARKS

This is in response to the Office Action mailed June 29, 2006, having a three-month shortened statutory period for reply set to expire September 29, 2006. Applicants respectfully request the reconsideration and allowance of the above-identified patent application. Please credit any overpayment or, alternatively, charge any fee deficiency to Deposit Account No. 13-2755.

Claims 1-83 are currently pending in the present application. Claims 12-20, 24-29, 31-44, 46-57, 59-72, and 74-83 have been withdrawn from consideration in accordance with an imposed restriction requirement. Claims 1-11, 21-23, 30, 45, 58, and 73 are under examination. Of the claims being examined, Claims 1-11 and 21-23 have been amended in efforts to advance prosecution on the merits, and claims 30, 45, 58 and 73 have been amended to incorporate the pertinent limitations of the claims to which they depended. No new matter has been added.

Applicants respectfully request reconsideration of the application in view of the foregoing amendments and the following remarks.

REJECTION UNDER 35 U.S.C. §112, Second Paragraph

Claims 1-11 and 21-23 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse.

The rejection was primarily based on the term "means", stating that it was unclear whether this was referring to an apparatus or a method.

Claims 1-11 and 21-23 have been amended to expressly recite the "method" described in the claims and supported by the specification.

Based on the foregoing, Applicants respectfully request the reconsideration, and withdrawal, of the rejection under 35 U.S.C. §112, second paragraph.

REJECTION UNDER 35 U.S.C. §102(e)

Claims 1-7 and 10 are rejected under 35 U.S.C. §102(e) as being anticipated by Mehtali *et al.*, U.S. Patent No. 6,475,480 (hereinafter "Mehtali *et al.*"). Mehtali. *et al.*, allegedly

teaches a method for propagating replication defective adenovirus in an E1-complementing cell line wherein a heterologous E4 region is inserted into an E1-deficient adenovirus and introducing the replication-defective adenovirus into an E1-complementing cell line. The argument rests primarily on a couple of statements in the disclosure where it is simply stated that heterologous E4 could be included in the vector, as well as on claim 8 where it states that the replication defective adenovirus can be Ad2 or Ad5. Based on this, the disclosure of Mehtali *et al.* was stated to anticipate the subject matter of claims 1-7 and 10. Applicants respectfully traverse.

Applicants submit first that the couple statements suggesting the use of heterologous E4 do not amount to a valid anticipatory teaching. In order to be a proper anticipatory reference, the cited reference would have to first meet all of the limitations of the rejected claims.

Claims 1-7 and 10 refer to a method for propagating adenovirus in an E1-complementing cell line, whereby the adenovirus being propagated contains a heterologous E4 region or portion thereof (comprising ORF6), said E4 region or portion thereof which is of the same serotype as that of the E1 of the complementing cell line. The claims also specifically state that the E1 of the cell line is non-native to the serotype of the adenovirus being propagated.

The only recitation in Mehtali *et al.* of the use of heterologous E4 sequence in replication defective adenovirus falls within a couple statements of the description indicating that alternative E4 sequences may be used which should still obtain the noted expression and/or persistence as seen when E4 is present. There is no teaching or suggestion that these cell lines could be propagated in a cell line that does not express E1 proteins of the same serotype as the replication defective adenovirus where the E1 sequence was deleted. In fact, the teachings within the specification would, quite to the contrary, lead one of skill in the art to employ a cell line that expresses an E1 region that is of the same serotype as the deleted E1 of the vector. First, Mehtali *et al.* teaches on col. 10, lines 5-19, that the replication-defective viruses can be propagated in complementation cell lines which supply in trans *the deleted/mutated viral functions*. Cell line 293 is mentioned as "commonly used" most likely because serotype 5 vectors are most frequently utilized as gene delivery vehicles. In fact, exemplification of the invention employed Ad5-based vectors with varying segments of Ad5 E4 deleted. The vectors were, thus, propagated in Ad5 E1, and Ad5E1/E4 complementing cell lines. The only other alternative discussed was the use of helper virus to complement at least part of the viral deficiencies in trans.

There is no teaching, either express or implied, that you could propagate a replication-defective adenovirus having a heterologous E4 region in a cell line that expresses an

E1 gene product of a serotype that is *different* from that of the replication-defective adenovirus, particularly by employing E4 sequence of the same serotype as the E1 region expressed by the cell line. Following the teachings of Mehtali *et al.*, one of skill in the art would think that the cell line need be tailored to the defective adenovirus, whether by use of the proper cell line supplying E1 or through an added helper virus to express the exact deleted function.

What, then, clearly is missing is what defines Applicants' invention - tailoring the defective adenovirus to the cell line, which is not a concept that is taught nor discussed anywhere in Mehtali *et al.*. To suggest such *necessarily* employs hindsight, a practice consistently frowned upon by the courts.

Claim 8 does not alter these arguments as claim 8 solely refers to the serotype of the replication-defective adenovirus being propagated, stating that it could either be Ad2 or Ad5. It does not speak to heterologous E4 nor does it speak to any particular propagation cell lines.

Applicants, therefore, respectfully request that the current rejection be closely reviewed. Applicants submit that no valid anticipation can be found based on the disclosure of Mehtali *et al.*. Critical elements forming Applicants' invention are lacking from the teachings therein; specifically, methods of propagating replication-defective adenoviruses in a cell line that expresses E1 that is not of the same serotype as the replication-defective adenovirus. In fact, guidance provided within the specification (*see above*) indicates that cell lines should be employed in the more traditional sense (using a cell line that expresses the deleted E1 region), the exact process that Applicants' invention very efficiently circumvents.

Accordingly, Mehtali *et al.* fail to disclose all of the elements of the rejected claims, as required for proper anticipation in accordance with 35 U.S.C. §102.

Applicants, therefore, respectfully request the reconsideration and withdrawal of the current rejection.

REJECTION UNDER 35 U.S.C. §103(a)

Claims 21-23 are rejected under 35 U.S.C. §103(a) as unpatentable over Mehtali *et al.* in view of Inglis *et al.*, U.S. Patent No. 5,665,362 (hereinafter, "Inglis *et al.*"). The disclosure of Inglis *et al.* is said to provide to Mehtali specific disclosure with regard to producing replication-defective adenovirus comprising a nucleotide encoding an HIV-1 gag antigen. Applicants respectfully traverse.

The presently rejected claims, claims 21-23, are focused on methods of propagating replication-defective adenoviral vectors in a cell line that expresses E1 of a serotype different from that of the replication-defective adenovirus.

There is no teaching or suggestion in Mehtali *et al.* that replication defective adenovirus comprising a heterologous E4 could be propagated in a cell line that expresses an E1 gene product of a serotype that is different from that of the replication defective adenovirus being propagated. In fact, the teachings within the specification would, quite to the contrary, lead one of skill in the art to employ a cell line that expresses an E1 region that is of the same serotype as the deleted E1 of the vector. Mehtali *et al.* teaches on col. 10, lines 5-19, that the replication-defective viruses can be propagated in complementation cell lines which supply in trans *the* deleted/mutated viral functions. There is no teaching or suggestion that this step could be circumvented other than through the use of a helper virus.

This significant deficiency in the teaching is, furthermore, not cured by the disclosure of Inglis *et al.* which merely cites adenovirus in a laundry list of vectors for attempted use in gene delivery and expression. The teachings of Mehtali *et al.* and Inglis *et al.*, therefore, either alone or in combination, do not render the present invention obvious. To suggest otherwise amounts to an inappropriate exercise of hindsight, a practice consistently frowned upon by the courts.

Accordingly, Applicants submit that the combination of references fall short of forming an appropriate §103 rejection.

Applicants, therefore, respectfully request the reconsideration and withdrawal of the present rejection.

REJECTION UNDER 35 U.S.C. §103(a)

Claim 6 is rejected under 35 U.S.C. §103(a) as unpatentable over Mehtali *et al.* in view of Li *et al.*, U.S. Patent No. 7,026,164 (hereinafter, "Li *et al.*"). The disclosure of Li *et al.* is said to provide to Mehtali specific disclosure regarding an Ad5 packaging cell line. Applicants respectfully traverse.

The presently rejected claim, claim 6, is focused on a method of propagating subgroup C replication-defective adenoviral vectors in a cell line that expresses E1 of a serotype different from that of the replication-defective adenovirus being propagated.

There is no teaching or suggestion in Mehtali *et al.* that a subgroup C replication defective adenovirus comprising a heterologous E4 could be propagated in a cell line that expresses an E1 gene product of a serotype *different* from that of the deleted E1 region. In fact, guidance within the specification would, quite to the contrary, lead one of skill in the art to employ a cell line that expresses the E1 region that is deleted from the replication defective adenovirus being propagated; *see, e.g.*, col. 10, lines 5-19, wherein the disclosure provides that

the replication-defective viruses can be propagated in complementation cell lines which supply in trans *the deleted/mutated viral functions*. There is no teaching or suggestion that this step could be circumvented other than through the use of a helper virus.

This significant deficiency in the teaching is, furthermore, not cured by the disclosure of Li *et al.* which is merely cited for the provision of an Ad5E1-expressing cell line.

Applicants, therefore, submit that the teachings either alone or in combination do not render the present invention obvious. To suggest otherwise amounts to an inappropriate exercise of hindsight, a practice consistently frowned upon by the courts.

Accordingly, Applicants submit that the combination of references fall short of forming an appropriate §103 rejection.

Applicants, therefore, respectfully request the reconsideration and withdrawal of the present rejection.

REJECTION UNDER 35 U.S.C. §103(a)

Claims 8 and 9 are rejected under 35 U.S.C. §103(a) as unpatentable over Mehtali *et al.* in view of Goosens *et al.*, 2001 *Arthritis & Rheumatism* 44:570-577 (hereinafter, "Goosens *et al.*"). Mehtali *et al.*, via claim 8, is said to "teach the use of combining serotypes Ad5 and Ad2 (vector found in claim 8, cell line described in col. 10, lines 5-10)". Goosens *et al.* is said to provide to Mehtali the disclosure of "chimeric adenoviruses based on Ad5 but carrying the DNA encoding adenovirus from subgroup B, including Ad11, Ad 16, and Ad35." Goosens *et al.* is also cited for producing the virus in PER.C6 cells. Applicants respectfully traverse.

The presently rejected claims, claims 8 and 9, are focused on methods for propagating subgroup B and serotype 35 replication-defective adenoviral vectors, respectively, in a cell line that expresses E1 of a serotype that is different than that of the replication-defective adenovirus being propagated.

There is no teaching or suggestion in Mehtali *et al.* that subgroup B or serotype 35 replication defective adenoviruses comprising a heterologous E4 of an alternative serotype could be propagated in a cell line that does not express the native E1 serotype of the adenoviruses being propagated. In fact, guidance within the specification would, quite to the contrary, lead one of skill in the art to employ a cell line that expresses the E1 region that is deleted from the replication defective adenovirus being propagated; *see, e.g.,* col. 10, lines 5-19, wherein the disclosure provides that the replication-defective viruses can be propagated in complementation cell lines which supply in trans *the deleted/mutated viral functions*. There is

no teaching or suggestion that this step could be circumvented other than through the use of a helper virus.

Claim 8 merely recites that the replication defective adenovirus can be Ad5 or Ad2. Taking the language of claim 8 to suggest an adenoviral vector with a heterologous E4 region is not appropriate. Nowhere in claim 8 is there any discussion or recitation of use of a heterologous E4. In addition, guidance as to a cell line is limited to the suggestion that the replication-defective viruses can be propagated in "a complementation cell line which supplies in trans *the deleted/mutated viral functions*" [*emphasis added*]. This does not, either expressly or impliedly, suggest or indicate that you could produce a vector in a cell line expressing E1 proteins of a distinct serotype by incorporation of an E4 region comprising a select component of E4 (ORF6).

Applicants further submit that Goosens does not supply this information. Goosens does not teach methods of propagating replication defective adenoviral vectors comprising a heterologous E4 region. Goosens discloses replication defective adenoviruses heterologous in their fiber domains. Chimeric vectors possessing the different fiber regions were generated in an Ad5 serotype vector deleted in *Ad5 E1 sequence* which were, notably, propagated in a cell line expressing *Ad5 E1*. This, further, instills the traditional method of propagating replication defective vectors in cell lines expressing the appropriate deleted E1 function of that virus.

Applicants, therefore, submit that the teachings either alone or in combination do not render the present invention obvious. To suggest otherwise amounts to an inappropriate exercise of hindsight, a practice consistently frowned upon by the courts.

Accordingly, Applicants submit that the combination of references fall short of forming an appropriate §103 rejection.

Applicants, therefore, respectfully request the reconsideration and withdrawal of the present rejection.

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Attached please find a Supplemental Information Disclosure Statement containing a reference cited in a Supplementary European Search Report.

In summary, Applicants maintain all claims are in condition for allowance and earnestly solicit a favorable action on the merits.

Respectfully submitted,

By _____

Anna L. Cocuzzo
Reg. No. 42,452
Attorney for Applicant

MERCK & CO., INC.
P.O. Box 2000
Rahway, New Jersey 07065-0907
(732) 594-1273

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